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Research in Specialization Studies in Industrial Pharmacy benefits pharmaceutical industry

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Summary

Several research projects in Industrial Pharmacy Specialization Studies have been finalized to the benefit of pharmaceutical industry. B. Sc. in Pharmacy working in pharmaceutical industry have done literature studies and developmental projects related to the topics of their daily work. For M.Sc. in Pharmacy, the research projects have resulted in licentiate thesis (2 scientific publications). The topics of the latest published research projects are development and usage of GMP auditing tool, development of Key Performance Indicators for quality assurance, outsourcing of regulatory affairs as well as effects of moxonidine and atenolol on insulin sensitivity, postmenopausal symptoms and blood pressure in hypertensive postmenopausal women.

Key words industrial pharmacy, specialization studies, auditing, key performance indicators, outsourcing, regulatory affairs

Introduction

Specialization Studies in Industrial Pharmacy are a postgraduate program for Master of Science (M. Sc.) and Bachelor of Science (B. Sc.) in Pharmacy working in pharmaceutical industry in Finland or abroad. Currently, this program is international (24% of our students are from abroad) and the call is open yearly in January-April. Since 1992, when the first Specialization Studies in Industrial Pharmacy started, several research projects have been conducted in University of Helsinki to the benefit of the society. For industrially employed M.Sc., these projects have been licentiate theses with the topics related to the students' daily work. These research projects have included either laboratory or qualitative research like surveys and interview studies. For B.Sc. the projects have been mostly literature studies on the topics related to their work descriptions or shorter development projects e.g. tools for daily work providing practical support for their working environments such as development of standard operation procedures, storage systems,

databases, methods etc. The literature studies done by B.Sc. have been valuable for the pharmaceutical companies to give a deeper knowledge on the focus areas of interest.

The research projects included in Specialization Studies in Industrial Pharmacy have been previously related to a licentiate thesis (i.e. requirement of two publications for M. Sc.). Since 2016, for M.Sc. students starting in the novel Specialization Studies in Industrial Pharmacy (ERKO), a research project should result in one article published in an international peer-reviewed journal (i.e. no Licentiate degree). This change was made due to the governmental change that removed the licentiate degree for Specialization Studies and changed them to this new type of Specialization Studies with a student fee and due to the fact that it is challenging to conduct academic research, while working full time in pharmaceutical industry. However, after finalizing the Specialization Studies in Industrial Pharmacy, it is possible to continue to the doctoral studies. An example of such project is Ph.D. (Pharm.) Kirsi Rosenqvist's dissertation project on the effect of systemically and locally administered clodronate on bone quality (Rosenqvist 2014).

To date, all together 57 B.Sc. and 9 Licentiate in Pharmacy have graduated from the Specialization Studies in Industrial Pharmacy from University of Helsinki. The last four licentiate theses, which have been finalized have had the following topics: 1) Anu Linna from Orion made her thesis on development and the use of Good Manufacturing Practise (GMP) audit preparation tool in pharmaceutical contract manufacturer audits in 2010; 2) Marianne Torkko from Orion investigated key performance indicators (KPIs) in quality management in 2014; 3) Satu Kujala from Medfiles studied the effects of moxonidine and atenolol on insulin sensitivity, postmenopausal symptoms and blood pressure in hypertensive postmenopausal women in 2016; and 4) Anu Gummerus working at DRA Consulting graduated with the topic Outsourcing Regulatory Affairs in Pharmaceutical Industry in 2017.

GMP Auditing of Contract Manufacturers

In Anu Linna's research project, the questionnaire tool for GMP auditing of contract manufacturers was developed (Linna et al. 2008, 2010). Firstly, the questionnaire was designed and validated with a Delphi method by getting feedback of the relevance of the questions asked from the GMP experts. In the second part, the objective was to evaluate the usefulness of the developed tool in audit preparation and during the actual GMP audit. Validity of the information given through the tool was examined by comparing the responses to the actual conditions observed during the contract manufacturer audits. Additionally, the contract manufacturers' opinions on the tool were gathered and the auditors were interviewed. The developed tool was proven to be useful in audit preparation phase from both the auditor's and the contract manufacturers' point of views. Furthermore, usage of the developed tool can save time when performing the audit. The results show that using the tool can give significant support in audit preparation phase and during the actual audit. These types of tools are nowadays regularly used in GMP audits.

Quality Key Performance Indicators for Pharmaceutical Industry

Marianne Torkko studied Key Performance Indicators (KPIs) in quality management (Torkko et al. 2013, 2014). Firstly, she studied what type of quality KPIs companies use and how they utilize the results of these KPIs in food and pharmaceutical industry. Quality KPIs were shown to be similar for both the pharmaceutical and food industries with some differences existing in their usage and reporting.

In the pharmaceutical industry, the most common quality KPI was rejected batches followed by number of complaints, product defects, and deviations. The number of complaints was the most common quality KPI for the food industry. The next most common KPIs were the loss during process and the number of

deviations. Respondents in both the pharmaceutical and food industries thought that it is important to follow the indicators that describe the quality of a product and operations. Food companies shared their KPIs and results with their partners and relevant authorities more often than pharmaceutical companies did. The results of this study showed that the food industry was slightly more advanced in the utilization of the quality indicators compared to the pharmaceutical industry. However, statistically significant differences exist between the pharmaceutical and food industries with regard to one quality indicator, namely rejected batches.

In the second part of the study, significance of quality KPIs and how comprehensively they are used in the pharmaceutical industry were studied. The specific aim was to find out those KPIs, which were relevant to personnel from the perspective of their own work responsibilities. The further aim was to determine which factors motivate personnel enough to respond to the improved KPIs. Qualitative theme interviews of ten staff members from one case company were conducted to study the impact of KPIs on the quality and operations in production. This interview data was analyzed using qualitative content analysis and reductive analysis.

Personnel considered deviations in manufacturing and packaging as the most important quality KPIs when they considered their own work responsibilities. The quality indicators data were utilized quite efficiently, for example, in complaint and deviation handling processes, and they provided useful information for corrective and preventive actions (CAPA) reporting. The most important factors that motivated supervisors, managers, and experts regarding KPIs were those that affected interviewees own particular work responsibilities, cooperation within the operators' own departments, and cooperation between different departments. The interviewees thought that the production bonus was the most important motivational factor for production operators to improve upon quality indicator performance. Quality indicator feedback data were utilized widely by the case company and were considered to be a useful tool to guide personnel in ensuring or potentially improving the quality of operations.

For this licentiate study of Torkko, the great interest has been shown especially from pharmaceutical industry. For example, Torkko's two articles have been read over 20 000 times in ResearchGate since 2014. This is an excellent example that the research done in Specialization Studies in Industrial Pharmacy is not only to the interest and benefit of the working environment locally or nationally but even internationally.

Medical Treatment of Hypertensive Postmenopausal Symptoms

Satu Kujala published two articles on her previous clinical studies at Algol on the effect of an imidazolin-1-agonist (moxonidine) and a beta-blocker (atenolol) on insulin sensitivity, postmenopausal symptoms and blood pressure in hypertensive postmenopausal women (Kaaja ym 2007, Kujala ym 2014). The aim was to compare the short-term effects of these two sympatholytic antihypertensive drug treatments, the peripherally acting β -blocking agent and the centrally acting imidazoline I_1 -receptor agonist in postmenopausal women with diastolic hypertension and obesity. Insulin sensitivity was measured by two different methods in subjects stratified by fasting plasma insulin level at baseline and by blood pressure response at the end of follow-up. In addition, the postmenopausal symptoms and their relationship to antihypertensive effect and the interaction between the effect on insulin sensitivity and menopausal symptoms were studied.

The severity of hot flushes and palpitations were reduced significantly in both treatment groups. In the atenolol treated group, one in every three patients (33%) reported relief from insomnia, and lightly fewer patients (27%) stated that their so-called General Impression of Symptoms (GIS) score was also significantly improved. The levels of irritability declined in blood pressure responders in the atenolol group. There was no correlation between the improvement in insulin sensitivity and the relief of postmenopausal symptoms.

This thesis is an example project from the early years of Specialization Studies when the industrial pharmacy research projects were started in collaboration with other disciplines, like pharmacology as in this case.

Outsourcing of Regulatory Affairs

Anu Gummerus investigated what kind of regulatory affairs tasks are outsourced, what are the reasons for outsourcing as well as the values and disadvantages of outsourcing these tasks in the pharmaceutical industry in the EU countries (Gummerus ym 2016a, 2016b). The aim was also to study to how many contract research organizations (CROs) pharmaceutical companies outsource their regulatory affairs tasks and duration of outsourcing partnerships between these companies.

According to the responses, 65% of the pharmaceutical companies have outsourced tasks related to research and development over the last three to five years. Over 44% of the respondents informed that they have outsourced to one or two CROs only. One quarter of the respondents have outsourced to three to five CROs. The principal reason for outsourcing regulatory affairs tasks to a CRO was the excessively heavy workload in the company's regulatory affairs. Also, outsourcing should be cost-effective.

The fact that a CRO has experience and knowledge was seen as a very important requirement when choosing the CRO partner. Personal, individual contacts were mentioned in many of the open-ended responses as an essential criterion in the selection of the CRO. Most (91%) of the respondents in the pharmaceutical industry strongly agree and agree on the fact that they outsource the regulatory affairs tasks because they want to obtain greater flexibility. The companies evaluated that outsourcing to CROs is expensive (strongly agree or agree 74%). CROs have to maintain the quality level high and obtain flexibility towards the outsourcing companies.

When a company is considering outsourcing regulatory tasks, planning has to be done well in advance. The main topics to be discussed between the outsourcing company and CRO before the outsourcing process are estimated costs of the outsourcing, outsourcing strategy, information flow and audit trails. Quality provided by CRO plays a significant role when the companies select their partner. The CRO has to assure uniform quality in their personnel knowledge and skills despite of personnel changes. Practically, all product development steps can be outsourced by local or multinational CROs. These Anu Gummerus' publications are also frequently read by international pharmaceutical industry (1700 reads since 2015 in ResearchGate).

On-going Research in Specialization Studies in Industrial Pharmacy

Since the students come from different types of pharmaceutical companies (i.e. small or big; originator or generic; CROs, wholesale or manufacturing) and additionally from the different functions within these companies, it is difficult to find larger themes for the research topics. The research projects are tailor-made for the students relating to their daily work or interest and the suitable supervisors and support will be organized for their specific needs.

Currently, there are altogether 30 research projects on going for M.Sc. and 20 studies for B.Sc. in industrial pharmacy. The great variety of topics for M.Sc. can be seen: nutraceuticals, customer research services for pharmaceutical industry, quality management system for regulatory affairs, medication faults related to dosing of medication in intensive care unit of neonates, authority practices in biosimilars, effect of lubricant, relative humidity and amount of sorbitol on compression of xylitol/sorbitol mixtures, work against drug counterfeiting and degradation of biopharmaceuticals with contact of reducing disaccharides, serialisation and pharmacovigilance.

The projects, which are related to a company's know-how, have to get a publication permission from the companies. Therefore, co-supervision of the scientific work has to be organized within the companies, too. This is sometimes challenging in smaller companies having no PhD as staff members. Further, the literature studies and research projects of B.Sc. have not been previously published, since students have not applied for publication permission from the companies. This will be developed in future, since the knowledge obtained in these projects might be useful for larger audience. There are plans to start publishing these

projects in the public university databases, which then requires publication permission from the companies. For literature studies this is not a problem, but for developmental projects this might be a challenge.

To conclude, all these research projects will give additional and deeper understanding on the current issues of the working environment for the students or tools to improve their daily work. These research projects have shown general interest not only in Finland but also internationally. Since 2008, industrial pharmacy has been a stand-alone discipline featuring research, development, manufacturing, marketing and distribution of pharmaceutical products as well as their related quality assurance. To our knowledge, this full academic discipline of industrial pharmacy with this scope is unique in the world.

Tiivistelmä

Teollisuusfarmasian erikoistumiskoulutuksen yhteydessä tehty tutkimus hyödyttää lääketeollisuutta

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Teollisuusfarmasian erikoistumiskoulutuksissa on tehty useita tutkimusprojekteja, jotka hyödyttävät lääketeollisuutta. Teollisuudessa työskentelevät farmaseutit ovat tehneet päivätöihinsä liittyviä kirjallisuusselvityksiä ja kehitysprojekteja ja proviisorit lisensointitöitä (2 osajulkaisua). Viimeisimpien julkaistujen tutkimusten aiheet ovat GMP-auditointityökalun kehittäminen, laatumittareiden kehittäminen laadunhallinnan työkaluksi, myyntilupatehtävien ulkoistaminen sekä moksonidiinin ja atenololin vaikutus insuliiniherkkyyteen, vaihdevuosisoireisiin ja verenpaineeseen vaihdevuosien jälkeen verenpainetautiä sairastavilla naisilla.

Avainsanat

teollisuusfarmasia, erikoistumiskoulutus, auditointi, laatumittari, ulkoistaminen, myyntiluparekisteröinti

Conflict of interest

Anne Juppo: Consultation in IPR matters for Orion Pharma, Finland 2017; Member of Scientific Committee of Orexo, Sweden 2017; EU project secondment, Zentiva, Czech Republic, 1 month in 2018

Mia Sívén: EU project secondment, APC, Ireland 1 month in 2018-2019; Invited speaker, Continuing Professional Development (CPD) event, Tamro, Finland 2018

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